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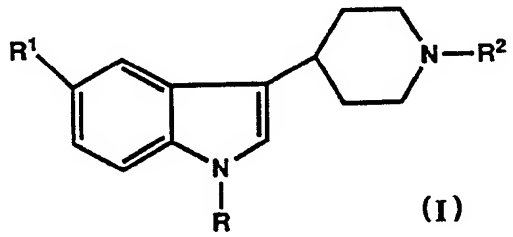
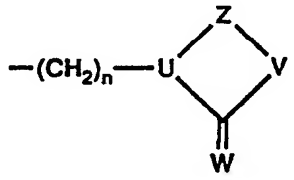


(I)



(IV)

(57) Abstract

1-Aryl-3-(4-piperidyl)-indole derivatives having general formula (I), wherein R^1 is hydrogen, halogen, alkyl, alkoxy, hydroxy, cyano, nitro, alkylthio, trifluoromethyl, trifluoromethylthio, alkylsulfonyl, amino, alkylamino or dialkylamino; R is optionally substituted phenyl or a heteroaromatic group; and R^2 is hydrogen, cycloalkyl, alkyl or alkenyl, optionally substituted with one or two hydroxy groups, or R^2 is a group of formula (IV), wherein n is an integer of from 2-6; W is O, S or N-R^3, wherein R^3 is H, alkyl or cycloalkyl; U is N or CH, Z is -$(CH_2)_m$-, m being 2 or 3, or Z is -CH=CH-, 1,2-phenylene, or -$COCH_2$- or -$CSCH_2$-; V is O, S, CH_2, or NR^4, wherein R^4 is hydrogen, optionally hydroxy substituted alkyl, alkenyl or cycloalkylmethyl; are useful in alleviating, relieving or suppressing withdrawal or abstinence symptoms or suppressing the dependency of a drug or a substance of abuse.

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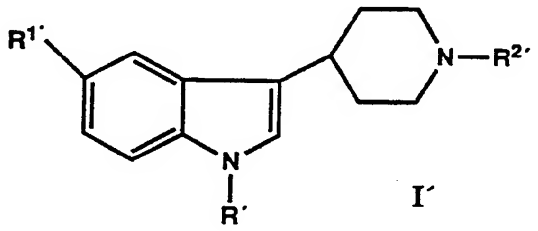
TREATMENT OF ADDICTION TO DRUGS AND SUBSTANCES OF ABUSE

Field of invention

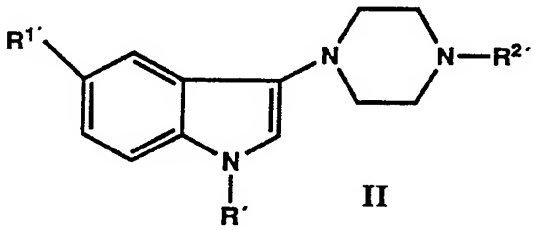
The present invention relates to the use of compounds belonging to a certain class of 1-aryl-3-(4-piperidyl)-indole derivatives for the treatment of addiction to drugs or substances of abuse such as alcohol or nicotine in man.

Background of the invention

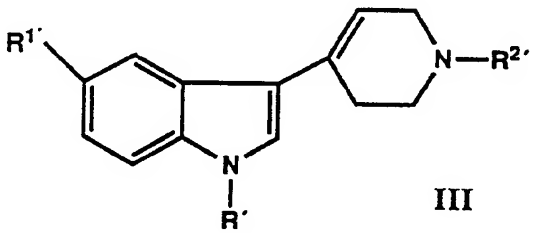
US patent No 4,710,500 corresponding to EP 200,322B, discloses in general optionally 5-substituted 1-aryl-3-(4-piperidyl)- (I′), 1-aryl-3-(1-piperazinyl)- (II) or 1-aryl-3-(1,2,3,6-tetrahydro-4-pyridyl)-indole (III) derivatives having the formulas:



I′



II



III

in which formulas R′ designates optionally substituted phenyl or a hetero aromatic group, $R^{1'}$ is hydrogen or a substituent such as halogen, alkyl, alkoxy, cyano, nitro, etc, and $R^{2'}$ is hydrogen, alkyl, alkenyl or a certain heterocycle-lower alkyl substituent.

Most of the compounds are shown to be potent and long-lasting dopamine antagonists *in vivo* , and accordingly to be useful in the treatment of psychoses and all the compounds are proven to be strong serotonin-S_2 (5-hydroxytryptamine-2;

5–HT_2) receptor antagonists *in vivo* indicating effects in the treatment of depression and negative symptoms of schizophrenia. The tests used to show blockade of dopaminergic activity *in vivo* were a catalepsy test and a methylphenidate test, both being at that time regarded as tests for dopaminergic activity. However, at present said two tests are considered also to be a measure of the propensity of an antipsychotic compound to induce extrapyramidal side effects.

Though US patent No 4,710,500 generally comprises the 3-(4-piperidyl) compounds of the Formula I′ disclosed above, only five such compounds have been specifically disclosed, i.e.1-(4-fluorophenyl)-5-methyl-3-(1-methyl-4-piperidyl)-1H-indole, hydrobromide, designated Lu 21-037,
1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, designated Lu 23-086,
1-(4-fluorophenyl)-3-[1-[2-(2-pyrrolidinon-1-yl)ethyl]-4-piperidyl]-5-trifluoro-methyl-1H-indole, fumarate, designated Lu 23-158,
1-(4-fluorophenyl)-3-(1-methyl-4-piperidyl)-5-trifluoromethyl-1H-indole oxalate, designated Lu 21-131,
5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, sertindole.

The compound sertindole which is the compound of the above Formula I′ wherin $R^{1'}$ is chloro, R′ is 4-fluorophenyl and $R^{2'}$ is 2-(2-imidazolidinon-1-yl)ethyl is a known neuroleptic, the neuroleptic activity of which is described in the co-pending US patent application No 07/508,240 corresponding to EP 392,959A.

Our copending International Patent Application Publ. No. WO 92/00070 discloses the 3-(4-piperidyl) compounds of the Formula I′ as having anxiolytic activity without cataleptic activity and our copending International Patent Application No. PCT/DK91/00291 describes prodrugs of sertindole.

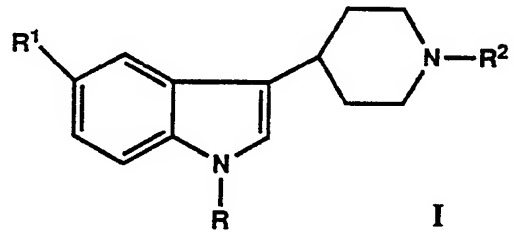
Addiction with physical and psychological dependence to drugs such as cocaine, opiates, benzodiazepines, etc, and abuse of alcohol and nicotine and other substances causes great social and health problems all over the world. When the drug or substance of abuse is withdrawn from a dependant subject the subject

develops physical and psychological withdrawal symptoms such as aggressive behaviour, agitation and intense craving for the drug or substance of abuse. Accordingly, withdrawal of such substances from addicts and abusers is very difficult, and no effective treatment of withdrawal symptoms and accordingly method of obtaining withdrawal is at present available. Accordingly, a compound which inhibits withdrawal symptoms or suppress dependence of drugs and other substances of abuse is highly desirable.

Surprisingly, it has now been found that certain 1-aryl-3-(4-piperidyl)-indole derivatives having the above general Formula I' in addition to the 5-HT_2 receptor antagonistic activity, also have alleviating, relieving or suppressing properties on withdrawal or abstinence symptoms and that they suppress the dependency of drug or substance of abuse. Furthermore they have been found to be non-cataleptic.

Disclosure of the invention

Accordingly the present invention provides the use of an 1-aryl-3-(4-piperidyl)-indole derivative having the generel formula:



I

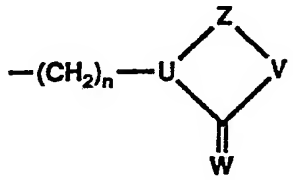
wherein

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, lower alkylthio, trifluoromethyl, trifluoromethylthio, lower alkylsulfonyl, amino, lower alkylamino or lower dialkylamino;

R is phenyl optionally substituted with one or more substituents independently selected from the following: halogen, lower alkyl, lower alkoxy, hydroxy, trifluoromethyl, and cyano, or R is 2-thienyl, 3-thienyl, 2-furoyl, 3-furoyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl; and

R^2 is hydrogen, cycloalkyl, lower alkyl or lower alkenyl, optionally substituted with

one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R^2 is a group of the Formula **IV** :



IV

wherein n is an integer of from 2 - 6, inclusive;

W is O, S or N-R^3, wherein R^3 is H, lower alkyl or cycloalkyl

U is N or CH;

Z is -$(CH_2)_m$-, m being 2 or 3, or Z is -CH=CH- or 1,2-phenylene optionally substituted with halogen or trifluoromethyl, or Z is -$COCH_2$- or -$CSCH_2$-;

V is O, S, CH_2, or NR^4 , wherein R^4 is hydrogen, lower alkyl optionally substituted with one or two hydroxy groups, lower alkenyl or a cycloalkylmethyl group, said cycloalkyl having from three to six carbon atoms inclusive;

or a pharmaceutically acceptable acid addition salt thereof or prodrug therefore for the manufacture of a pharmaceutical preparation for alleviating, relieving or suppressing withdrawal or abstinence symptoms or suppressing the dependency of a drug or a substance of abuse.

In another aspect the present invention provides a method for alleviating, relieving or suppressing withdrawal or abstinence symptoms or suppressing the dependency of a drug or a substance of abuse comprising the step of administering a therapeutically effective amount of a compound having the Formula I as defined above to a person in need thereof.

The drugs causing the withdrawal symptoms may be opiates, such as morphine and heroine, cocaine, amphetamine, and benzodiazepines, such as diazepam, clonazepam, and nitrazepam, etc. In particular, the substances of abuse may be nicotine and alcohol.

The term "lower alkyl" is intended to mean a straight or branched alkyl group having

from one to four carbon atoms, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, etc. Lower alkoxy, lower alkylthio, lower alkylsulfonyl, lower alkylamino and lower dialkylamino similarly designate such groups wherein the alkyl moiety is a lower alkyl group as defined above.

The term cycloalkyl designates a carbocyclic ring having 3-8 carbon atoms inclusive.

Lower alkenyl is intended to mean an alkenyl group containing from 2 to 4 carbon atoms, for example ethenyl, 1-propenyl, 2-butenyl, etc.

The Z-group $-COCH_2-$ or $-CSCH_2-$ may be oriented in either direction in the ring.

Some of the compounds of the general Formula I may exist in optical isomers thereof; and the administration of such optical isomers is also embraced by the method of the invention.

The Prodrugs used in the present invention may be conventional esters with available hydroxy groups, or in particular if the compound is a compound of the general Formula I wherein W is oxygen and V is $>NR^4$, R^4 being hydrogen, the prodrug may be formed by acylating the nitrogenatom of the V group and being accordingly represented by the Formula I wherein W is oxygen and V is $>N-R^{4'}$ wherein $R^{4'}$ designates a group **–A–B**,

wherein A is selected from CO, CS, or CH_2, and

if A is CO or CS, B is selected from the groups consisting of:

i) hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl or cycloalk(en)ylalk(en)yl, optionally substituted with one or two hydroxy groups, or phenyl optionally substituted with one or more substituents selected from the group consisting of halogen, trifluoromethyl, lower alkyl, lower alkoxy, lower alkylthio, acyloxy, or cyano; or

ii) QR^5, wherein Q is O or S and R^5 is selected from the substituents defined for B under i) above; and

iii) NR^6R^7, wherein R^6 and R^7 independently are selected from the substituents

defined for B under i) above, or R^6 and R^7 are combined to form a four to eight membered heterocyclic ring containing from one to three nitrogen atoms and from zero to three oxygen or sulfur atoms; or

if A is CH_2, B is selected from the groups consisting of:

iv) a group QR^5 as defined in ii);

v) a group NR^6R^7 as defined in iii); or

vi) a group $OC(O)R^8$, wherein R^8 is as defined for B under i).

Although the latter prodrugs are not esters , they have been found to decompose properly in order to release the compound of the invention over an desired period of time when administered parenterally as a depote formulation in an apropriate oil, such as coconut oil, e.g. viscoleo®, peanut oil, sesame oil, cotton seed oil, corn oil, soy bean oil, olive oil, etc. or synthetic esters of fatty acids and glycerol or propyleneglycol.

The pharmaceutically acceptable acid addition salts of the compounds used in the invention are salts formed with non-toxic organic or inorganic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The compounds of the Formula I and the pharmaceutically acceptable acid addition salts thereof may be administered in any suitable way, e.g. orally or parenterally, and the compounds may be presented in any suitable form for such administration, eg. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection.

An effective daily dose of a compound of the Formula I or a pharmaceutically acceptable salt thereof may be from 1.0 µg/Kg to 1.0 mg/Kg body weight.

The compounds used in the method of the invention have been found to show effects in *in vivo* drug, and substance of abuse withdrawal tests in mice, and they have been found not to induce catalepsy or only induce weak catalepsy (cf. Our Internat. Patent Application Publ. No. WO 92/00070) which is today regarded as indicative of extrapyramidal side effects. It is indeed very surprising that the present compounds are non-cataleptic whereas the compounds of the Formulas **II** and **III** of the above US patent have proved to be cataleptic (c.f. the pharmacological data in the following) and the mechanisms behind this are not fully understood. Accordingly the compounds of the present invention are believed to be useful in the treatment of addiction to drugs and substances of abuse, particularly in the relieving or alleviating the withdrawal symptoms and reducing the dependency, without causing the extrapyramidal side effects known from tradtional psychotropics.

Certain imidazolyl-pyridoindol and Imidazolyl-azepinoindol compounds known to be selective 5-HT_3 receptor antagonists and alleged to have anxiolytic effects have been disclosed also to have effects on withdrawal of drugs and other substances of abuse, EP Patent Publication No. 357 415 A2. However, the compounds used in the present invention which have also been found to be anxiolytic (c.f our copending International Patent Application Publ. No. WO 92/00070) are very different chemical structures without effects on the 5-HT_3 receptor in the brain. Furthermore it is known that other anxiolytics, such as the benzodiazepines, do not show effects in the above mentioned tests. Additionally the known anxiolytic buspirone do not counteract abstinence syndrome (Schweizer and Rickels, Am. J. Psychiat., **143**: 1590-1592 (1986)). Accordingly, the mechanisms of action on withdrawal symptoms are either different from those of the compounds of EP Patent Publication No. 357 415 A2 or they are due to common activities not known.

Brief description af the drawings

Figures **1 a-d** illustrate the effect of administration of a compound of the invention, i.e. sertindole in a dose of 0.1mg/kg i.p., on withdrawal symptoms following diazepam treatment.

Figures **2 a-d** illustrate the effect of administration of a compound of the invention, i.e. sertindole in a dose of 0.1mg/kg i.p., on nicotine withdrawal symptoms.

Figures **3 a-d** illustrate the effect of administration of a compound of the invention, i.e. sertindole in a dose of 0.1mg/kg i.p., on cocaine withdrawal symptoms.

Figures **4 a-d** illustrate the effect of administration of a compound of the invention, i.e. sertindole in a dose of 0.1mg/kg i.p., on alcohol withdrawal symptoms.

Detailed description of the invention.

In a preferred embodyment of the invention the compound used is a compound of the Formula **I** as defined in the foregoing wherein

R is phenyl substituted in 4 position with fluoro, or R is 2- or 3- thienyl;

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, cyano, trifluoromethyl, or lower alkylsulphonyl;

R^2 is a group having the Formula **IV** as defined in the foregoing wherein

n = 2 - 6 ;

W is O or S;

U is N;

Z is $-(CH_2)_2-$, $-(CH_2)_3-$, or -CH=CH-; and

V is O, CH_2 or NR^4, R^4 being hydrogen or lower alkyl;

or a pharmaceutically acceptable acid addition salt thereof or prodrug therefor.

A particularly preferred compound used in the invention is the compound of formula wherin R^1 is chloro, R is 4-fluorophenyl and R^2 is 2-(2-imidazolidinon-1-yl)ethyl known as sertindole.

The compounds of the Formula **I** used in the invention may be prepared according to methods (b), (c), or (d) described in US patent No. 4,710,500. 2-pyrrolidinthiones are prepared from the corresponding lactame derivatives according to litterature methods (Bull.Soc.Chim.Belg. **87**, 223, 229, 299, 525 (1978)) by using Lawesson´s reagent or phosphorous pentasulphide at appropriate tempera-

tures. Imidazolidin-2-thion derivatives are prepared by ringclosure reactions from properly substituted ethylendiamines with carbondisulphide, thiophosgen or corresponding thiocarbonyl precursor compounds.

5-Hydroxy substituted indoles are prepared by conventional methods of demethylation of the coresponding methyl ethers. Pyridine hydrochloride or hydrobromide or methionin in methanesulphonic acid is used to split off the methyl group.

The 5-cyano compounds are prepared by substitution of 5-bromo or 5-iodo in the appropriate substituted compounds using CuCN in an aprotic polar solvent such as N,N-dimethylformamide, N-methyl-2-pyrrolidone (NMP) or HMPA at elevated temperatures.

The acid addition salts of the compounds used in the invention are easily prepared by methods well known in the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or an excess of the acid in an aqueous immiscible solvent such as ethyl ether or chloroform with the desired salt separating directly. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts.

In addition to the substances specifically mentioned in US patent No 4,710,500, specific examples of compounds used according to the invention are the following compounds which were prepared according to methods (b), (c), or (d) described in US patent No. 4,710,500 or from the corresponding lactame derivatives according to litterature methods (Bull.Soc.Chim.Belg. **87**, 223, 229, 299, 525 (1978)) by using Lawesson´s reagent or phosphorous pentasulphide at appropriate temperatures:

5-chloro-1-(4-fluorophenyl)-3-[1-(2-hydroxyethyl)-4-piperidyl]-1H-indole, hydrochloride, **1** MP : 266-269° C

5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-oxazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, fumarate, **2**, MP : 203-205° C

5-chloro-1-(4-fluorophenyl)-3-[1-[2-(3-methyl-2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, fumarate, **3**, MP : 198-199° C

5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-pyrrolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, fumarate, **4**, MP : 209-211° C

1-(4-fluorophenyl)-3-[1-[2-(3-methyl-2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-5-trifluoromethyl-1H-indole, **5**, MP : 144-145° C

1-(4-fluorophenyl)-3-[1-[2-(2-oxazolidinon-1-yl)ethyl]-4-piperidyl]-5-triflouromethyl-1H-indole, fumarate, **6**, MP : 212-213° C

5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-pyrrolidinthion-1-yl)ethyl]-4-piperidyl]-1H-indole, fumarate, **7**, MP : 195-199° C

1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-5-methylsulfonyl-1H-indole, fumarate, **8**, MP : 188-192° C

5-chloro-1-(4-fluorophenyl)-3-[1-[6-(2-pyrrolidinon-1-yl)-1-hexyl]-4-piperidyl]-1H-indole,hydrochloride, **9**, MP : 123-128° C

5-chloro-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole, fumarate, **10** , MP: 196-201°C

1-(4-fluorophenyl)-3-(4-piperidyl)-5-trifluoromethyl-1H-indole, hydrochloride, **11** MP : 281-284° C

1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-5-trifluoromethyl-1H-indole, **12**, MP : 169-171° C

1-(4-fluorophenyl)-3-[1-[6-(2-pyrrolidinon-1-yl)-1-hexyl]-4-piperidyl]-5-trifluoromethyl-1H-indole,oxalate, **13**, MP : 85-87° C

5-chloro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, oxalate, **14**, MP : 92-96° C

5-fluoro-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole, fumarate, **15**, MP: 198-200 °C

5-fluoro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, oxalate, **16**, MP : 188-190° C

5-fluoro-1-(4-fluorophenyl)-3-[1-[2-(2-pyrrolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, fumarate, **17**, MP : 178-180° C

5-fluoro-1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, fumarate, **18**, MP : 115-120° C

5-chloro-1-(4-fluorophenyl)-3-[1-[5-(2-imidazolidinon-1-yl)-1-pentyl]-4-piperidyl]-1H-indole, oxalate, **19**, MP : 145-147° C

5-chloro-1-(4-fluorophenyl)-3-[1-[4-(2-imidazolidinon-1-yl)-1-butyl]-4-piperidyl]-1H-indole, oxalate, **20**, MP : 178-179° C

5-chloro-1-(4-fluorophenyl)-3-[1-[6-(2-imidazolidinon-1-yl)-1-hexyl]-4-piperidyl]-1H-indole, oxalate, **21**, MP : 156-158° C

5-chloro-1-(4-fluorophenyl)-3-[1-[2-(hydantoin-2-yl)ethyl]-4-piperidyl]-1H-indole, **22**, MP : 174-176° C

5-fluoro-1-(4-fluorophenyl)-3-[1-[6-(2-pyrrolidinon-1-yl)-1-hexyl]-4-piperidyl]-1H-indole, **23**, oil

1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-5-methyl-1H-indole, **24**, MP : 187-189° C

1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-5-methyl-1H-indole, hydrochloride, hydrate, **25**, MP : 214-215° C

1-(4-fluorophenyl)-3-[1-[2-(2-pyrrolidinon-1-yl)ethyl]-4-piperidyl]-5-methyl-1H-indole, hydrochloride, hemihydrate, **26**, 265-266°C

1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-5-trifluoromethyl-1H-indole, **27**, MP : 99-100° C

3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1-(3-thienyl)-1H-indole, oxalate **28**, MP : 139-140° C'

1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-5-methoxy-1H-indole, **29**, MP : 167° C

5-fluoro-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1-(3-thienyl)-1H-indole, oxalate, hemihydrate, **30**, MP : 95-97° C

5-fluoro-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1-(2-thienyl)-1H-indole, dioxalate, **31**, MP : 173-174° C

5-bromo-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **32**, MP : 171-172° C

1-(4-fluorophenyl)-3-[1-[2-[3-(2-propyl)-2-imidazolidinon-1-yl]ethyl]-4-piperidyl]-1H-indole, hydrochloride, **33**, MP : 226-227° C

5-chloro-1-(4-fluorophenyl)-3-[1-[3-(2-imidazolidinon-1-yl)-1-propyl]-4-piperidyl]-1H-indole, fumarate, **34**, MP : 203-205° C

In the following examples the preparation of an imidazolidin-2-thion derivative and of two derivatives having a hydroxyl and a cyano group, respectively, in the 5-position of the indole ring is shown :

EXAMPLE 1

5-chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinthion-1-yl)ethyl]-4-piperidyl]-1H-indole, oxalate, **35**, MP : 150° C

To a solution of 5-chloro-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole (25 g) in N-methyl-2-pyrrolidone (150 ml) were added chloroacetonitrile (6 g) and triethylamine (10 ml). The reaction mixture was heated at 60° C for one hour and subsequently poured onto crushed ice. The precipitated 5-chloro-3-(1-cyanomethyl-4-piperidyl)-1-(4-fluorophenyl)-1H-indole was filtered off and washed with water. Yield 20 g. MP : 170-172° C.

A solution of the thus isolated cyanomethylderivative (24 g) in dry THF (150 ml) was added dropwise to a previously prepared solution of AlH_3 (from 8 g of $LiAlH_4$ and 8 g of $AlCl_3$) in dry diethyl ether (250 ml). The mixture was heated at reflux for one hour and finally hydrolyzed by carefully adding a conc. aqueous solution of NaOH (10 ml) under simultaneous cooling. Inorganic salts were filtered off and were subsequently carefully washed with hot dichloromethane (2 x 100 ml). the combined organic phases were dried (anh. $MgSO_4$) and finally evaporated leaving 3-[1-(2-aminoethyl)-4-piperidyl]-5-chloro-1-(4-fluorophenyl)-1H-indole (25 g) as an oil. Without further purification this product (12 g) and triethylamine (4.2 g) were heated in 1,1,1-trichloroethane (100 ml) at 50-55° C. A solution of chloroacetonitrile (3.6 g) in 1,1,1-trichloroethane (10 ml) were added dropwise during 10 minutes. The mixture was heated for another 4 hours at 50° C. Ethyl acetate (200 ml) was added and the mixture was poured into ice cooled dil. aqueous NaOH solution (400 ml). The organic phase was separated, washed with brine, dried (anh. $MgSO_4$) and the solvents evaporated leaving 5-chloro-3-[1-[2-(N-cyanomethyl)aminoethyl]-4-piperidyl]-1-(4-fluorophenyl)-1H-indole (14 g) as an oil.

The oil thus isolated was dissolved in dry THF (100 ml) and added dropwise to a previously prepared solution of AlH_3 (from 6 g of $LiAlH_4$ and 6 g of $AlCl_3$) in dry diethyl ether (200 ml). The mixture was refluxed for one hour and finally hydrolyzed by cautiously adding a conc. aqueous solution of NaOH (8 ml) under simultaneous

cooling. Inorganic salts were filtered off and were subsequently washed with hot dichloromethane (2 x 100 ml). The combined organic phases were dried (anh. $MgSO_4$) and finally evaporated leaving 3-[1-[N-(2-aminoethyl)-2-aminoethyl]-4-piperidyl]-5-chloro-1-(4-fluorophenyl)-1H-indole (8.5 g) as an oil. This oil (4.5 g) was dissolved in 1-pentanol (50 ml) and carbondisulphide (5 ml) was added. After stirring for 2 hours at room temperature the resulting suspension was heated to 140° C for 1.5 hours. Excess CS_2 was flushed away by a gentle stream of N_2 gas. Finally most of the 1-pentanol was evaporated at reduced pressure. The remaining oil was purified by column chromatography on silica gel (eluted with ethyl acetate/ ethanol/triethylamine - 80/20/4). The oxalate salt of the title compound **35** crystallized from acetone.

Yield 250 mg. MP: 150° C.

EXAMPLE 2

1-(4-Fluorophenyl)-5-hydroxy-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole. **36**, MP: 220°C

Pyridinhydrochloride (60 g) and 1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-5-methoxy-1H-indole, compound **29** (6 g) were mixed and heated to 180°C under N_2 for 1 1/2 hours. After cooling, water (300 ml) and ethyl acetate (100 ml) were added. By addition of NH_4OH solution the pH was adjusted to >9. The organic phase was separated, washed with water (50 ml), dried (anh. $MgSO_4$), and the solvent evaporated leaving the phenolic crude title compound as an oil. Purification by column chromatography on silica gel (eluted with ethyl acetate/dichloromethane/ethanol/triethylamine 60:20:20:5) afforded the title compound **36** as a crystalline material. Yield: 1.9 g. MP: 220°C.

EXAMPLE 3

5-Cyano-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-4-piperidyl]-1H-indole, **37**, MP: 209°C.

To a solution of 5-bromo-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole (17 g) in dichloromethane (170 ml) was added a solution of ditert. -butyloxycarbonate (12 g) in dichloromethane (30 ml). After stirring for 30 minutes at room temperature the dichloromethane was evaporated in vacuo. 5-Bromo-3-(1-tert-butyloxycarbonyl-4-piperidyl)-1-(4-fluorophenyl)-1H-indole crystallized from n-heptane. Yield: 14 g. MP: 155°C. All the crystalline material was dissolved in N-methyl-2-pyrrolidone (75 ml) and CaCN (5 g) was added. The mixture was heated at 160°C for 6 hours. The mixture was then poured into a solution of NaCN (10 g) in water (200 ml) and stirred for 20 minutes. Diethyl ether (200 ml) was added. The ether phase was separated, washed with brine (50 ml), dried (anh. $MgSO_4$), and the ether evaporated leaving a mixture of 5-bromo and 5-cyano compounds which were separated by coloumn chromatography on silica gel (eluted with diethyl ether). The 3-(1-tert.butyloxycarbonyl-4-piperidyl)-5-cyano-1-(4-fluorophenyl)-1H-indole was isolated an an oil. Yield: 4.5 g. The protecting group - tert.butyloxycarbonyl - was splitted off by standard acidic (CF_3COOH) decomposition. The thus obtained 5-cyano-1-(4-fluorophenyl)-3-(4-piperidyl)-1H-indole (3.2 g) was dissolved in methyl isobutyl ketone (90 ml). Potassium carbonate (4.5 g), potassium iodide (0.5 g) and 1-(2-chloroethyl)-2-imidazolidinone (2.3 g) were added. The mixture was refluxed for 16 hours. After cooling inorganic salts were filtered off, and the organic solvent evaporated. Water (100 ml) and ethyl acetate (50 ml) were added. The organic phase was separated, dried (anh. $MgSO_4$), and finally ethyl acetate evaporated leaving the crude title compound as an oil. Purification by column chromatography on silica gel (eluted with ethyl acetate / ethanol / triethylamine 80:20:4) afforded 2.1 g of pure crystalline title compound, **37**. MP: 209°C.

PHARMACOLOGY

The compounds used in the invention were tested in accordance with well recognized and reliable test methods. The tests were as follows:

CATALEPSY TEST

Evaluation of catalepsy is made according to Arnt (Eur. J. Pharmacol. 90, 47 -55 (1983)). Test compound is given s.c. in different doses. The rat (170 - 240 g) is placed on a vertical wire mesh (mesh diameter 12 mm). The rat is considered cataleptic if it remains immobile for more than 15 sec. The maximum number of rats showing catalepsy within the first 6 hours is recorded for each dose group. The results are recorded in fractions and an ED_{50} value is calculated by means of log-probit analysis. The results are shown in Table **1** (cf. Our Internat. Patent Application Publ. No. WO 92/00070).

The following corresponding 1-aryl-3-(1,2,3,6-tetrahydrpyridyl)- or 1-aryl-3-(piperazinyl)indole derivatives which are analogues of sertindole and compound No 12, respectively, were included in the test as comparing compounds:

1-(4-Fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydropyridin-4-yl]-5-trifluoromethyl-1H-indole (Comp. A)

5-Chloro-1-(4-fluorophenyl)-3-[1-[2-(2-imidazolidinon-1-yl)ethyl]-1,2,3,6-tetrahydro-4-pyridyl]-1H-indole (Comp. B)

5-Chloro-1-(4-fluorophenyl)-3-[4-[2-(2-imidazolidinon-1-yl)ethyl]-1-piperazinyl]-1H-indole (Comp. C)

TABLE 1

Cataleptic Activity

Compound	ED50(s.c.) (μmol/kg)
Sertindole	>98
Comp. No 12	38
Comp. No 2	>18
Comp. No 3	31
Comp. No 4	23
Comp. No 14	>69
Comp. No 16	>78
Comp. No 24	>95
Comp. A	0.49
Comp. B	2.2
Comp. C	4.5

Further ED_{50} values of corresponding 1-aryl-3-(1,2,3,6-tetrahydro-4-pyridyl)- or 1-aryl-3-(1-piperazinyl)indole derivatives are given in US patent No 4,710,500.

INHIBITION OF WITHDRAWAL SYMPTOMS IN MICE

The tests are tests for the effect of a substance on the abstinence symptoms induced by withdrawal of a drug or a substance of abuse in mice measured as the effect on some specific behavioral changes following to withdrawal of the drug or substance of abuse. Such an animal model has been shown to be indicative of effects on withdrawal symptoms (Barry et al. Pharmac. Biochem. Behav. **27**: 239-245 and Costall et al. Pharmac. Biochem. Behav., **33**, 1989, 197, and Kelly et al. Eur. Neurosci. Ass. Winter Scool Meet. Zuos, Switzerland, 10-17th Jan. 1987) .

Materials.

The test was conducted using an open-top experimental box (45*27*27cm) two fifths of which was partitioned from the rest, painted black and illuminated with a dim red light (1 x 60 W, zero Lux). The remainder of the box was painted white and brightly illuminated (60 W, 400 Lux) with a white light source. The light sources were located 17 cm above the box and the base of the box was lined into 9 cm squares. Access between the two compartments was by means of a 7.5 x 7.5cm opening located in floor level at the centre of the partition.

The mice were male BKW mice having weight of 25-30g, housed in groups of 10 and given free acces to drink and food and kept on a dark/light cycle of 12 hours.

A) Diazepam withdrawal

Diazepam (10 mg/kg) was given i.p. twice a day for 7 days and then withdrawn. At the time of the last dose the mice received test substance, and on the following day they received a dose of test substance at 8 a.m. and another 40 min. prior to testing.

The test was carried out by taking the mice to a dimly illuminated room and then after 1 hour adaption to the new environment placing them in the centre of the white section of the test box. Behavioural changes were assed via remote video recording. The following behavioural changes were measured :

a) The time spent in the white and black section;
b) the number of explorative rearings in both the white and black section;
c) the number of line crossings in the white and black section; and
d) the latency of the initial movement from the white to the black area.

Separate groups of mice were used for each behavioural assesment and the experiment was carried out blind. The control group represent the mean control data for 15 mice.

The results are shown graphically in Figure 1 for one compound according to the invention, i.e. sertindole, administrated in a dose of 0.1 mg/kg.

B) Nicotine withdrawal

The experimental design was as described for the diazepam withdrawal studies. Nicotine was given (0.1mg/kg i.p., b.d) for 7 days and test compound was given with the last dose of nicotine. Animals were tested on the following day after receiving a total of 3 doses of test compound. The assesment of the behavioural changes was as described for diazepam.

The results are shown graphically in Figure **2** for one compound according to the invention, i.e. sertindole, administrated in a dose of 0.1 mg/kg.

C) Cocaine withdrawal

The experimental design was as described for the diazepam withdrawal studies. Cocaine was given (1mg/kg i.p., b.d) for 14 days and test compound was given during withdrawal for 24 hours (i.p., b.d). The assesment of the behavioural changes was as described for diazepam.

The results are shown graphically in Figure **3** for one compound according to the invention, i.e. sertindole, administrated in a dose of 0.1 mg/kg.

D) Alcohol withdrawal

The experimental design was as described for the diazepam withdrawal studies. Alcohol was given for 14 days (8% in drinking water) and withdrawn for 24 hours. Test compound was given during withdrawal (i.p., b.d). The assesment of the behavioural changes was as described for diazepam.

The results are shown graphically in Figure **4** for one compound according to the invention, i.e. sertindole, administrated in a dose of 0.1 mg/kg.

It appears from Table **1** that the compounds of the invention are without or substantially without cataleptic activity and accordinly being lacking the extrapyramidal side effects probably associated with the corresponding known 3-(1,2,3,6-tetrahydro-4-pyridyl) and 3-(1-piperazinyl) derivatives.

It is clearly demonstrated in Figure **1** and **2** that the compound according to the invention has a marked relieving effect on the symptoms following to the withdrawal of diazepam and nicotine, respectively. So, the test compound is seen to have a statistically significant inhibiting effect on the withdrawal behavioural changes both as regards diazepam and nicotine.

FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting maschine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulations of the invention are as follows:

1) Tablets containing 0,5 milligrams of sertindole calculated as the free base:

Sertindole	0.5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 1 milligrams of compound No 3 calculated as the free base:

Comp. **3**	1.0 mg
Lactose	16 mg
Potato starch	45 mg
Sacc´harose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

Comp. **16**	5.0 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

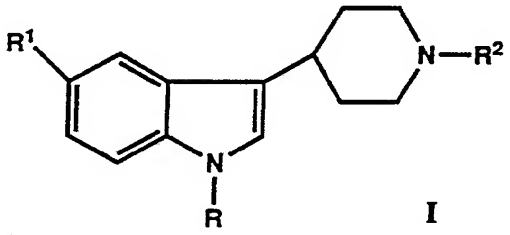
Sertindole	0.2 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:

Comp. **3**	0.5 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

CLAIMS

1. Use of an 1-aryl-3-(4-piperidyl)-indole derivative having the generel formula:



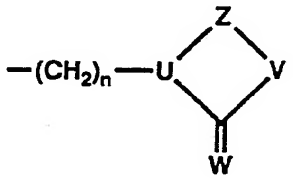
I

wherein

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, cyano, nitro, lower alkylthio, trifluoromethyl, trifluoromethylthio, lower alkylsulfonyl, amino, lower alkylamino or lower dialkylamino;

R is phenyl optionally substituted with one or more substituents independently selected from the following: halogen, lower alkyl, lower alkoxy, hydroxy, trifluoromethyl, and cyano, or R is 2-thienyl, 3-thienyl, 2-furoyl, 3-furoyl, 2-thiazolyl, 2-oxazolyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, or 4-pyridyl; and

R^2 is hydrogen, cycloalkyl, lower alkyl or lower alkenyl, optionally substituted with one or two hydroxy groups, any hydroxy group present being optionally esterified with an aliphatic carboxylic acid having from two to twentyfour carbon atoms inclusive, or R^2 is a group of the Formula **IV** :



IV

wherein n is an integer of from 2 - 6, inclusive;

W is O, S or N-R^3, wherein R^3 is H, lower alkyl or cycloalkyl

U is N or CH;

Z is $-(CH_2)_m-$, m being 2 or 3, or Z is -CH=CH- or 1,2-phenylene optionally substituted with halogen or trifluoromethyl, or Z is $-COCH_2-$ or $-CSCH_2-$;

V is O, S, CH_2, or NR^4 , wherein R^4 is hydrogen, lower alkyl optionally substituted with one or two hydroxy groups, lower alkenyl or a cycloalkylmethyl group, said

cycloalkyl having from three to six carbon atoms inclusive;
or a pharmaceutically acceptable acid addition salt thereof or prodrug therefore for the manufacture of a pharmaceutical preparation for alleviating, relieving or suppressing withdrawal or abstinence symptoms or suppressing the dependency of a drug or a substance of abuse.

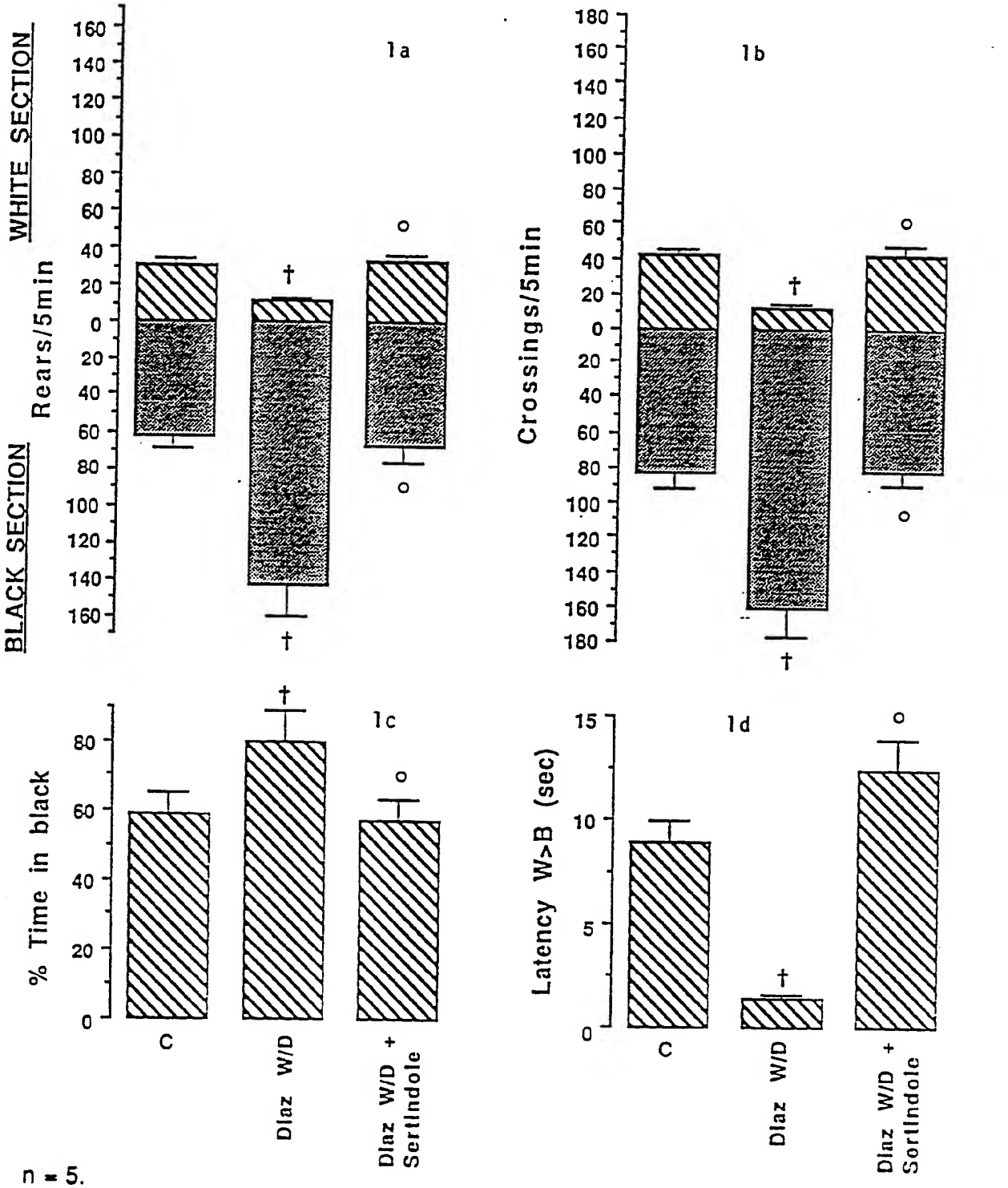
2. Use according to Claim **1**, **characterised in that** the compound used is a compound of the general Formula **1** as defined in Claim **1** wherein
R is phenyl substituted in 4 position with fluoro, or R is 2- or 3- thienyl;
R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, cyano, trifluoromethyl, or lower alkylsulphonyl;
R^2 is a group having the Formula **IV** as defined in the foregoing wherein
n = 2 - 6 ;
W is O or S;
U is N;
Z is $-(CH_2)_2-$, $-(CH_2)_3-$, or -CH=CH-; and
V is O, CH_2 or NR^4, R^4 being hydrogen or lower alkyl;
or a pharmaceutically acceptable acid addition salt thereof or prodrug therefor.

3. Use according to Claim **1** or **2**, **characterised in that** the pharmaceutical preparation is for alleviating, relieving or suppressing the withdrawal or abstinence symptoms or suppressing the dependency of cocaine, diazepam, nicotine or alcohol.

4. A method for alleviating, relieving or suppressing withdrawal or abstinence symptoms or suppressing the dependency of a drug or a substance of abuse comprising the step of administering a therapeutically effective amount of a compound having the Formula **I** as defined in Claim **1** to a person in need thereof.

FIG. 1 1/4

Influence of test compound on withdrawal symptoms following diazepam treatment



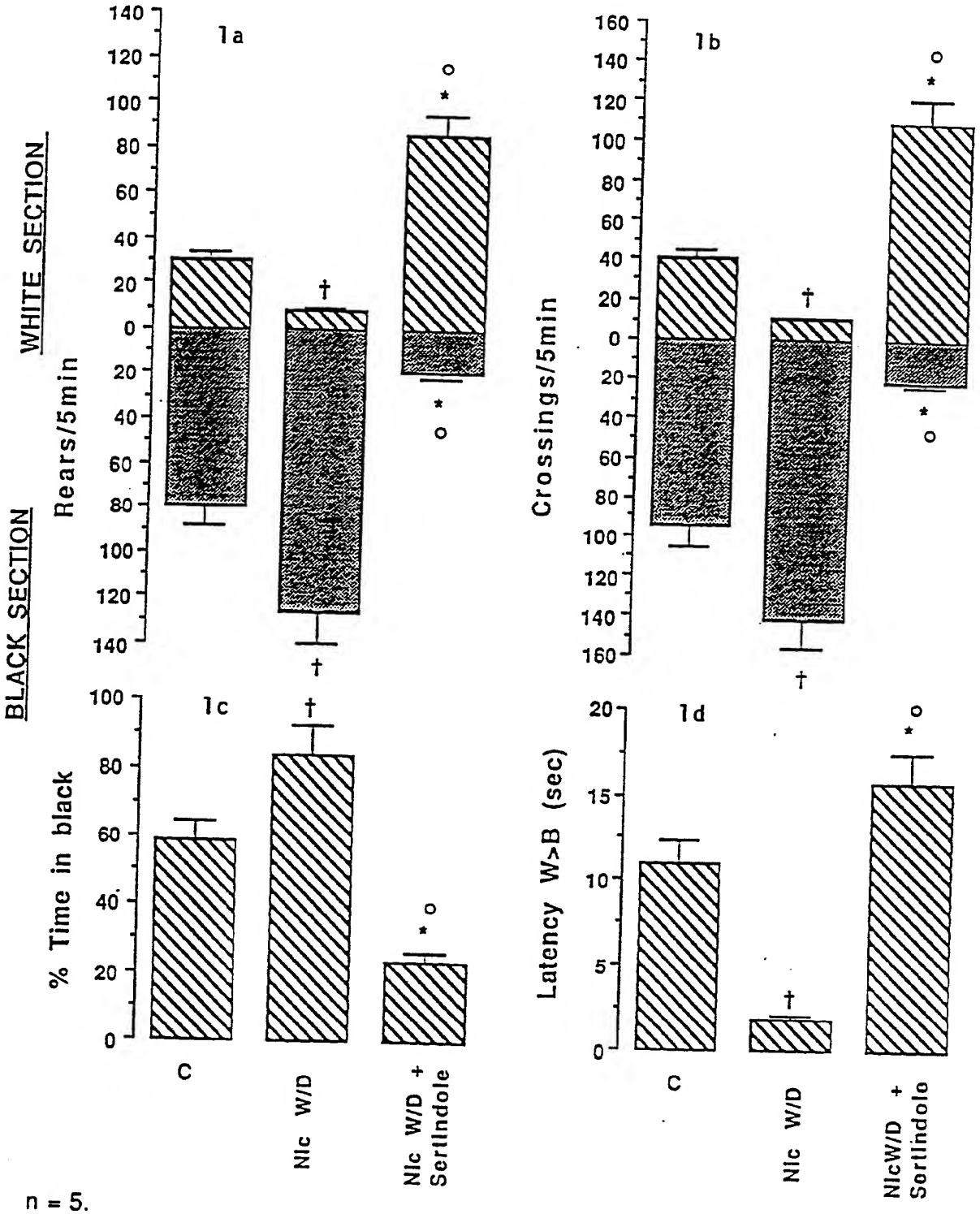
n = 5.

(Diaz) Diazepam given at 10mg/kg i.p. for 7 days and (W/D) withdrawn for 24 h. Test compound was given during withdrawal at 0.1mg/kg i.p. b.d.

† P < 0.001 (changes from control). ○ P < 0.001 (reversal withdrawal symptoms)

FIG. 2

Influence of test compound on nicotine withdrawal symptoms

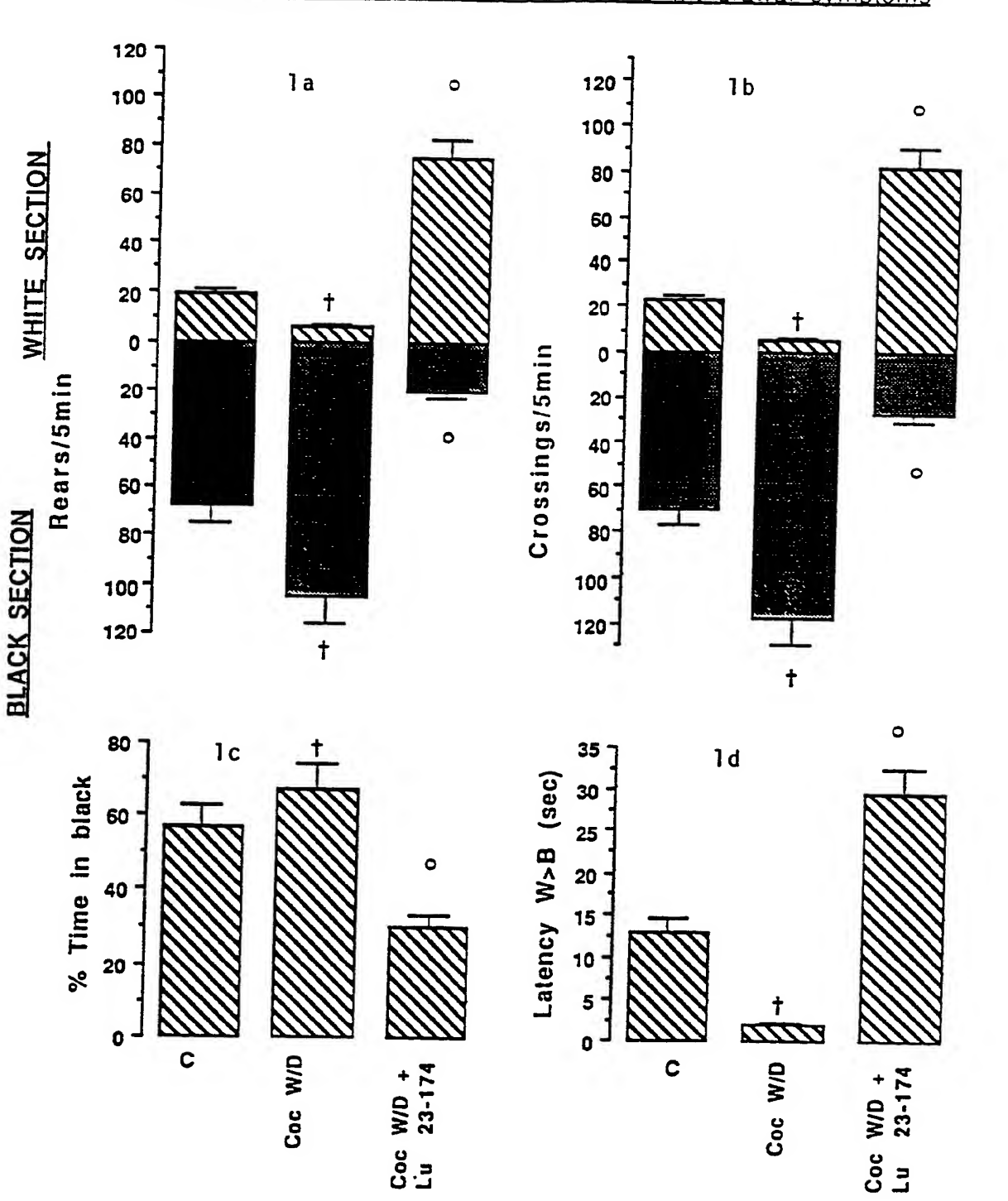


n = 5.

(Nic) Nicotine given at 0.1mg/kg i.p. for 7 days and (W/D) withdrawn for 24 h. Test compound was given during withdrawal at 0.1mg/kg i.p. b.d.

† P < 0.001 (changes from control). ° P < 0.001 (reversal withdrawal symptoms)

FIG. 3

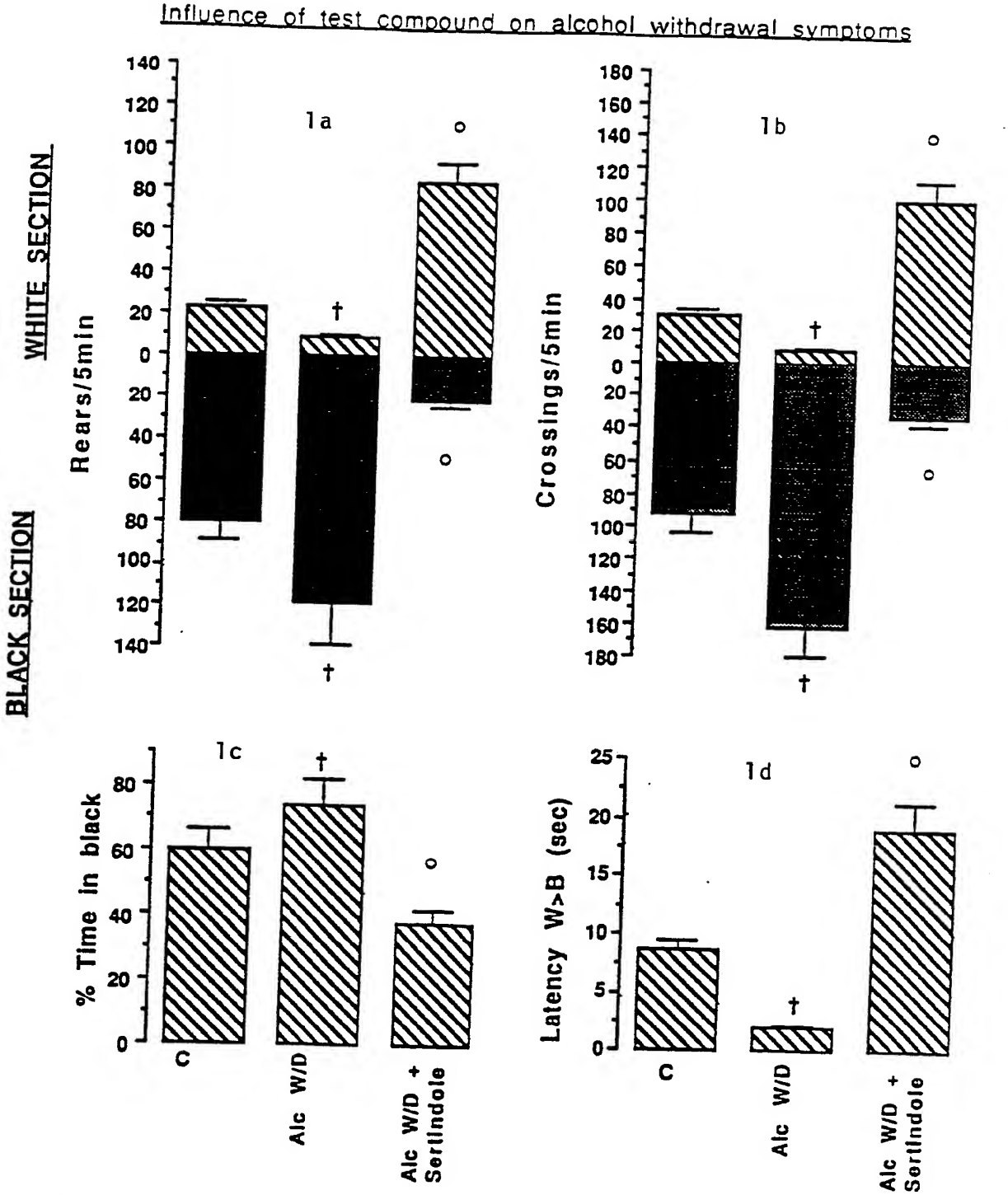


n = 5.

(Coc) Cocaine given at 1mg/kg i.p. for 14 days and (W/D) withdrawn for 24 h. Test compound was given during withdrawal at 0.1mg/kg i.p. b.d.

† P < 0.001 (changes from control). ○ P < 0.001 (reversal withdrawal symptoms)

FIG. 4



n = 5.

(Alc) Alcohol given for 14 days 8% w/v in drinking water and (W/D) withdrawn for 24 h.

Test compound was given during withdrawal at 0.1mg/kg i.p. b.d.

† $P < 0.001$ (changes from control). ○ $P < 0.001$ (reversal withdrawal symptoms)

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 92/00062

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/445

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO, A2, 9004387 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 3 May 1990, see page 9, line 4 --	1-3
A	US, A, 4710500 (PERREGARD) 1 December 1987, see the whole document --	1-3
	It is pointed out that the basis for the A-category is that a known compound may in many countries be claimed by a product claim restricted to the first medical use and in many of these countries by a use claim for other medical indications. (Second medical indication). --	
	--------	

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1st June 1992	1992 -06- 09
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Anna Sjölund

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers.....4....., because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 92/00062

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 30/04/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A2- 9004387	90-05-03	CA-A-	2001572	90-04-26
		EP-A-	0440704	91-08-14
		US-A-	4999382	91-03-12
US-A- 4710500	87-12-01	AU-B-	583607	89-05-04
		CA-A-	1256437	89-06-27
		EP-A-B-	0200322	86-11-05
		JP-A-	61236764	86-10-22